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IN THE UNITED STATES PATENT AND TRADEMARK OFFICE

IN RE APPLICATION OF

SCHUURMAN ET AL.

APPLICATION NO:

FILED:

FOR: COMBINATIONS OF IMMUNOSUPPRESSIVE AGENTS FOR THE
TREATMENT OR PREVENTION OF GRAFT REJECTIONS

Assistant Commissioner for Patents
Washington, DC 20231

CLAIM OF PRIORITY UNDER 35 USC §119

Sir:

Applicants in the above-identified application hereby claim priority under the International Convention of Great Britain Application No. 9910835.9, filed on May 10, 1999, and Great Britain Application No. 9925443.5, filed on October 27, 1999. These applications are acknowledged in the Declaration of the instant case.

The certified copies of said applications are submitted herewith.

Respectfully submitted,

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Date: *November 7, 2001*

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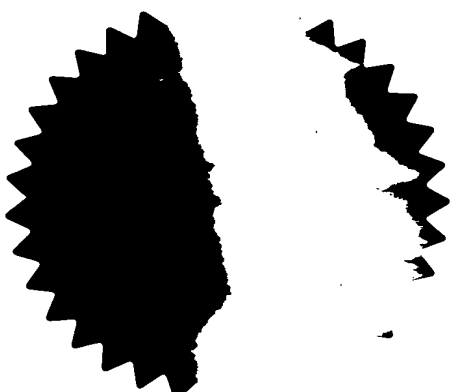
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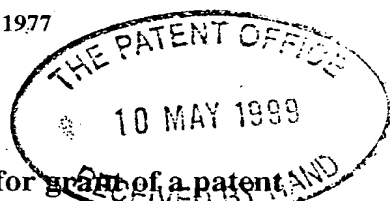
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Description **11**

Claim(s) **2**

Abstract **1**

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Organic Compounds

This invention is concerned with certain novel pharmaceutical compositions comprising combinations of immunosuppressive agents and the use of such compositions for the treatment or prevention of xenograft rejection.

In order for xenotransplantation to present a clinically viable treatment for organ disease, it is necessary to effectively treat or prevent acute rejection and chronic rejection of donor organs. Effective treatments need to inhibit T-cells and also B-cell-mediated or antibody-mediated rejection.

However, a problem associated with combining compounds that suppress T-cells as well as compounds that act against B-cell-mediated rejection or antibody-mediated rejection is the potential and unpredictable pharmacokinetic interaction of the compounds which may influence the toxicity or the immunosuppression of the combination.

Surprisingly, the applicant has found that pharmaceutical compositions comprising certain combinations of immunosuppressant compounds display good tolerability whilst at the same time display prolonged xenograft survival of donor organs, few rejection episodes and good graft function.

Accordingly, the invention provides in one of its aspects a pharmaceutical composition useful in the prevention or treatment of xenograft rejection comprising combinations of immunosuppressant compounds selected from the group consisting of an IL-2 transcription inhibitor and immunosuppressant compounds that immunosuppress for B-cell-mediated or antibody-mediated rejection of xenografts.

A more preferred pharmaceutical composition according to the invention comprises combinations of mycophenolic acid (MPA), pharmaceutically acceptable salts and esters of MPA, for example the sodium salt of MPA and the mofetil ester of MPA, rapamycin and derivatives thereof including 40-O-(2-hydroxyethyl)-rapamycin, and IL-2 transcription inhibitors.

Most preferred pharmaceutical compositions according to the invention comprise double combinations of MPA sodium salt and cyclosporine or 40-O-(2-hydroxyethyl)-rapamycin, the double combination of cyclosporine and 40-O-(2-hydroxyethyl)-rapamycin, or a triple combination of MPA sodium salt, cyclosporine and 40-O-(2-hydroxyethyl)-rapamycin.

Pharmaceutical compositions according to the invention act synergistically, i.e. the immunosuppressive effect of the combination of compounds is greater than additive. This has the advantage that relatively low doses of each compound may be used in the pharmaceutical compositions. Synergy may be calculated according to a method described in Berenbaum, Clin. Exp. Immunol. (1977) 28:1.

The term "IL-2 transcription inhibitor" as used hereinabove refers to immunosuppressive compounds whose immunosuppressive activity derives principally or in significant part from their direct or indirect inhibition of IL-2 gene transcription, e.g. corticosteroids, ascomycins and cyclosporines, FK506 and their various derivatives and analogues.

Cyclosporine, (also known as cyclosporin A or cyclosporin) is an immunosuppressive cyclic undecapeptide. Its structure is disclosed, e.g. in the Merck Index, 11th edition; Merck & Co. Inc., Rahway, New Jersey, USA (1989) under listing 2759. Formulations of cyclosporine are commercially available under the trademark SANDIMMUN or SANDIMMUNE and a microemulsion preconcentrate formulation of cyclosporine is sold under the trademark NEORAL or OPTORAL.

A preferred rapamycin derivative referred to hereinabove is 40-O-(2-hydroxyethyl)-rapamycin. 40-O-(2-hydroxyethyl)-rapamycin is a rapamycin derivative the structure of which is disclosed in WO 94/09010, example 8, and is a semi-synthetic derivative of rapamycin. The structure of rapamycin is given in Kessler, H., et al.; 1993; Helv. Chim. Acta; 76; 117, and numerous immunosuppressive derivatives and analogues of rapamycin are known.

MPA and its mofetil ester are known immunosuppressants. MPA sodium salt is known and is disclosed in published patent application No. WO 97/38689.

The indications for which the pharmaceutical compositions may be useful are conditions associated with, or causal to, transplant rejection, for example treatment (including amelioration, reduction, elimination or cure of etiology or symptoms) or prevention (including substantial or complete restriction, prophylaxis or avoidance) of xenograft rejection, including acute and chronic rejection of an organ when the organ donor is of a different species from the recipient, most especially rejection mediated by B-cells or antibody-mediated rejection.

The invention therefore provides in another of its aspects a method of treatment of a condition as hereinabove described comprising the administration to a patient in need of such treatment, of a pharmaceutical composition comprising combinations of immunosuppressant compounds selected from the group consisting of an IL-2 transcription inhibitor and immunosuppressant compounds that immunosuppress for B-cell-mediated or antibody-mediated rejection of xenografts.

More particularly the method comprises the administration of a pharmaceutical composition comprising combinations of mycophenolic acid (MPA), pharmaceutically acceptable salts and esters of MPA, for example the sodium salt of MPA and the mofetil ester of MPA, rapamycin and derivatives thereof including 40-O-(2-hydroxyethyl)-rapamycin, and IL-2 transcription inhibitors.

Preferably the method comprises the administration of a pharmaceutical composition comprising combinations of MPA sodium salt and one or more immunosuppressant compounds selected from the group consisting of an IL-2 transcription inhibitor, especially cyclosporine, and rapamycin and derivatives thereof, especially 40-O-(2-hydroxyethyl)-rapamycin.

In a further aspect of the invention there is provided the use of a pharmaceutical composition comprising compounds selected from the group consisting of an IL-2 transcription inhibitor and immunosuppressant compounds that immunosuppress for B-cell-mediated or antibody-mediated rejection of xenografts, in the treatment of a condition as hereinabove described.

More particularly the invention provides the use of a pharmaceutical composition comprising combinations of mycophenolic acid (MPA), pharmaceutically acceptable salts and esters of MPA, for example the sodium salt of MPA and the mofetil ester of MPA, rapamycin and

derivatives thereof including 40-O-(2-hydroxyethyl)-rapamycin, and IL-2 transcription inhibitors, in the treatment of a condition as hereinabove described.

Preferably the invention provides the use of a pharmaceutical composition comprising combinations of MPA sodium salt and one or more immunosuppressant compounds selected from the group consisting of an IL-2 transcription inhibitor, especially cyclosporine, and rapamycin and derivatives thereof, especially 40-O-(2-hydroxyethyl)-rapamycin, in the treatment of a condition as hereinabove described.

In yet another aspect of the invention there is provided a kit-of-parts comprising any of the pharmaceutical compositions hereinabove described, especially a pharmaceutical composition comprising MPA sodium salt and one or more immunosuppressant compounds selected from the group consisting of an IL-2 transcription inhibitor, especially cyclosporine, and rapamycin and derivatives thereof, especially 40-O-(2-hydroxyethyl)-rapamycin, together with instructions for use in the treatment or prevention of a condition as hereinabove described.

The dosages of the compounds will vary depending on the individual to be treated, the route of administration and the nature and severity of the condition to be treated. For example, in the prevention or treatment of xenograft rejection, an initial dose of about 2 to 3 times the maintenance dose may suitably be administered about 4 to 12 hours before transplantation, followed by a daily dosage of 2 to 3 times the maintenance dosage for one to two weeks, before gradually tapering down the dose at a rate of about 5% per week to reach the maintenance dose.

The exact dosage of each compound may be determined having regard to the particular therapeutic blood levels required for each compound. Thus, through judicious selection of the dosage of each compound, surprisingly it has been found that pharmaceutical compositions may be formed that are tolerated and which display synergistic action in immune suppression.

Accordingly, in another aspect of the invention there is provided a pharmaceutical composition comprising an IL-2 transcription inhibitor, in particular cyclosporine, that may be delivered to a patient at a dosage such that the 16 hour blood trough level is up to 500ng per

ml, for example 50 to 500 ng per ml, more particularly 100 to 500ng per ml, e.g. 300 to 500 ng per ml, and an immunosuppressant compound that immunosuppresses for B-cell-mediated or antibody-mediated rejection of xenografts that may be delivered to a patient at a dosage such that the 16 hour blood trough level is 1 to 10, preferably 3 to 6 micrograms per ml of the active substance, or is 10 to 35ng per ml, more particularly 10 to 20ng per ml.

In particularly preferred pharmaceutical compositions, mycophenolic acid (MPA), pharmaceutically acceptable salts and esters of MPA, for example the sodium salt of MPA and the mofetil ester of MPA, especially MPA sodium salt, may be delivered to a patient at a dosage such that the 16 hour blood trough level is, 1 to 10, preferably 3 to 6 micrograms per ml of MPA. IL-2 transcription inhibitors, e.g. cyclosporine may be delivered to a patient at a dosage such that the 16 hour blood trough level of, e.g. cyclosporine is up to 500ng per ml, for example 50 to 500 ng per ml, more particularly 100 to 500ng per ml, e.g. 300 to 500 ng per ml. Rapamycin and derivatives thereof, e.g. 40-O-(2-hydroxyethyl)-rapamycin may be delivered to a patient at a dosage such that the 16 hour blood trough level of, e.g. 40-O-(2-hydroxyethyl)-rapamycin is 10 to 35ng per ml, more particularly 10 to 20ng per ml.

The blood concentrations hereinabove described may be determined according to any convenient method known in the art. For example, blood may be collected in EDTA-coated containers, and detection of blood levels may be carried out by, e.g. radioimmunoassay or by ELISA. Detection of MPA is suitably carried out after protein precipitation using acetonitrile using an HPLC method with UV detection at 305nm. From the data collected in this way, the blood trough levels may be calculated by methods known in the art.

Having regard to the blood trough levels stated hereinabove, the skilled person may determine those dosages that provide a therapeutic amount of compound at a level that is tolerated and which exhibits synergistic action in immune suppression.

The weight ratio of component compounds of the pharmaceutical compositions may vary having regard to the desired blood trough levels stated hereinabove.

Pharmaceutical compositions may comprise combinations of an IL-2 transcription inhibitor and an immunosuppressant compound or compounds that immunosuppresses for B-cell-

mediated or antibody-mediated rejection of xenografts in a weight ratio of about 1:50 to 200:1, more particularly 1:2 to 50:1, e.g. 10:1. When more than one compound that immunosuppresses for B-cell-mediated or antibody-mediated rejection of xenografts is employed, for example in the case of a triple combination, the combined weight of said immunosuppressant compounds is reflected in the aforementioned weight ratio.

In a preferred embodiment a pharmaceutical composition comprises MPA sodium salt and cyclosporine in a weight ratio of about 1 : 0.03 to about 1 : 0.5.

In another preferred embodiment a pharmaceutical composition comprises MPA sodium salt and 40-O-(2-hydroxyethyl)-rapamycin in a weight ratio of about 1 : 0.0005 to 0.015, to 1:0.001 to 0.0075, in particular, 1: 0.0025.

In a particularly preferred pharmaceutical composition comprising the double combination of MPA sodium salt and cyclosporine, MPA sodium salt may be applied at a dosage of 10 to 100mg/kg/day, preferably 20 to 60mg/kg/day, in particular 40 to 60mg/kg/day; whereas cyclosporine may be applied at a dosage of 10 to 50mg/kg/day, preferably 10 to 15, mg/kg/day, in particular 3 to 6mg/kg/day. Most preferably MPA sodium salt may be applied at a dosage of 20mg/kg/day and cyclosporine may be applied at a dosage of 10mg/kg/day.

In another particularly preferred pharmaceutical composition comprising a double combination of MPA sodium salt and 40-O-(2-hydroxyethyl)-rapamycin, MPA may be applied at dosages referred to in the preceding paragraph, whereas 40-O-(2- hydroxyethyl)-rapamycin may be applied at a dosage of from 0.05 to 1.5mg/kg/day, e.g. 0.1 to 0.75mg/kg/day, e.g. 0.25 to 0.5mg/kg/day. Most preferably MPA sodium salt may be applied at a dosage of 20mg/kg/day and 40-O-(2-hydroxyethyl)-rapamycin may be applied at a dosage of 1.5mg/kg/day.

In yet another particularly preferred pharmaceutical composition comprising a double combination of cyclosporine and 40-O-(2-hydroxyethyl)-rapamycin, cyclosporine may be applied at a dosage of 10 to 50mg/kg/day, preferably 10 to 15, mg/kg/day, in particular 3 to 6mg/kg/day; whereas 40-O-(2-hydroxyethyl)-rapamycin may be applied at a dosage of 0.05 to 1.5mg/kg/day, e.g. 0.1 to 0.75mg/kg/day, e.g. 0.25 to 0.5mg/kg/day.

In yet another particularly preferred pharmaceutical composition comprising the triple combination aforementioned, MPA sodium salt may be applied at a dosage of 10 to 100mg/kg/day, preferably 20 to 60mg/kg/day, in particular 40 to 60mg/kg/day; cyclosporine may be applied at a dosage of 10 to 50mg/kg/day, preferably 10 to 15, mg/kg/day, in particular 3 to 6mg/kg/day; and 40-O-(2-hydroxyethyl)-rapamycin may be applied at a dosage of from 0.05 to 1.5mg/kg/day, e.g. 0.1 to 0.75mg/kg/day, e.g. 0.25 to 0.5mg/kg/day. Most preferably MPA sodium salt may be applied at a dosage of 20mg/kg/day and 40-O-(2-hydroxyethyl)-rapamycin may be applied at a dosage of 1.5mg/kg/day; and cyclosporine may be applied at a dosage of 10mg/kg/day.

The dosages referred to hereinabove may be administered to a patient in any convenient way, for example individual dosages referred to hereinabove may be administered daily in 2 divided doses. Any regimen may be used, provided that therapeutic amounts of the individual compounds are delivered to the patient.

The application of the pharmaceutical composition may be preceded by the administration of a suitable induction therapy, chosen from any suitable induction therapy known in the art, for example a short course of cyclophosphamide, e.g. 20 to 40 mg/kg i.v. per day for 4 days. Furthermore, a tapering course of steroids, e.g. methylprednisolone at a concentration of 1mg/kg at day one tapering to a baseline of 0.2mg/kg/day may be administered.

The compounds hereinabove described may be used in pharmaceutical compositions according to the invention in free or fixed combination, preferably in free combination. By 'free' is meant that each compound is formulated separately in a discrete dosage form. By 'fixed' is mean that the compounds are formulated together in one carrier. As a further embodiment, the pharmaceutical compositions may be both free and fixed whereby two or more compounds may be formulated in a single carrier whereas a further compound of the pharmaceutical composition may be formulated as a discrete dosage form.

Where one or more of the compounds are formulated separately, the individual dosage forms may be taken together or substantially at the same time (e.g. within fifteen minutes or less) so that, in the case of oral administration for example, said compounds are present simultaneously in the stomach.

The pharmaceutical composition according to the invention may be formulated in any convenient dosage form, the component compounds being either in a single carrier or formulated as discrete dosage forms as in a free combination, for example oral dosage forms, e.g. solid oral dosage forms or solutions or dispersions, or in forms suitable for intravenous administration.

Pharmaceutical compositions for oral administration of, e.g. cyclosporine and/or 40-O-(2-hydroxyethyl)-rapamycin, are suitably emulsions, microemulsions, preconcentrates of either, or solid dispersions, especially water-in-oil microemulsion preconcentrates or oil-in-water microemulsions.

Cyclosporine may be formulated in any of the ways known in the art, in particular the known microemulsion preconcentrate formulations of cyclosporine are particularly suitable for use in the present invention.

40-O-(2-hydroxyethyl)-rapamycin may be formulated in any of the ways known in the art, for example as a microemulsion (see WO 96/13273), as a fat emulsion for use in intravenous administration (see WO 97/25977), as a suspension (see WO 96/13239) or as a solid oral dosage form, for example, as a co-precipitate with a suitable carrier medium (a so-called solid dispersion) as more fully described in WO 97/03654 all of which documents are incorporated herein by reference.

MPA sodium salt may be formulated in any of the ways described in WO 97/38689 which is incorporated herein by reference, in particular as a solid oral dosage form, e.g. an enteric-coated tablet.

Pharmaceutical compositions according to the invention are useful as therapies in the treatment or prevention of xenograft rejection, including acute or chronic rejection of an organ from a discordant species, e.g. heart, lung, combined heart-lung, liver and kidney, most especially when the rejection is mediated by B-cells or antibodies.

There now follows a series of examples which are illustrative of the invention.

Example 1. Organ Xenograft Studies: Porcine Kidney to Cynomolgus Monkey

Cynomolgus monkeys undergo heterotopic renal transplants using porcine kidneys transgenic for hDAF.

Immunosuppression consists of induction therapy consisting of cyclophosphamide and a tapering course of steroids followed by maintenance therapy with free combinations of cyclosporine and MPA sodium salt as set forth in the Table below.

Induction therapy consists of four daily intravenous injections of cyclophosphamide (40mg/kg) and methylprednisolone low dose treatment (1mg/kg) day one and thereafter reducing the dose each day by 0.05mg/kg, and subsequently to a baseline dose of 0.02mg/kg/day as part of the maintenance therapy.

Maintenance therapy, subsequent to the induction therapy, consists of cyclosporine (Neoral®) and MPA sodium salt (MPA Na in the Table) in the form of a powder in a 1% methylcellulose (Courtauld's Chemicals) solution.

Dosing occurs twice daily at 8am and 4pm and the doses set forth in the Table are equally divided for that purpose. Dosing is carried out by gastric gavage under slight ketamine anaesthesia (10mg/kg) in a volume of 2ml/kg of body weight followed by flushing with at least 10ml/kg physiological saline.

Table 1.

Tolerability of combinations of MPA Sodium and Cyclosporine in Cynomolgus Monkeys. (Dosages in mg/kg).

MPA Na	Cyclosporine ²	Outcome
50 <i>bid</i>	25 <i>bid</i>	Tolerated
100 <i>bid</i>	25 <i>bid</i>	Tolerated
40+60 ¹	30 <i>bid</i>	Tolerated

¹ First dose at 7 am, second at 3 pm

bid = Twice per day

² Neoral[®]

Significant prolongation of the xenografts treated with the foregoing combinations were observed compared with monotherapy of the individual compounds of the combinations.

Example 2. Organ Xenograft Studies: Hamster-to-Rat

Donor male Chinese hamsters are obtained from Tongji Medical University.

Recipient male SD rats are obtained from Tongji Medical University.

Maintenance therapy consists of MPA sodium in the form of a powder in a 1% methylcellulose (Courtauld's Chemicals) solution, cyclosporine (Neoral[®]), and/or 40-O-(2-hydroxyethyl)-rapamycin in the form of a solid dispersion at 9.09% by weight, together with HPMC (81.82% by weight) and lactose (9.09% by weight).

All compounds are freshly prepared before administration and dissolved in distilled water. The compounds are administered daily per oral by gavage (<2ml/kg body weight).

Anaesthesia is carried out using Hypnorm and Hypnovel i.v. anaesthesia.

Table 2 illustrates significant prolongation of xenografts using compositions according to the invention.

Treatment Schedule (mg/kg/day)	Graft survival (days)	n
MPA sodium salt (20) Cyclosporine A (10)	5,5,6,6,6,14	6
MPA Sodium salt (20) 40-O-(2-hydroxyethyl)-rapamycin (1.5)	6,7,7,11,16,17	6
MPA Sodium salt (20) 40-O-(2-hydroxyethyl)-rapamycin (1.5) Cyclosporine A (10)	6,7,10,10,12	5

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Claims

1. Pharmaceutical composition useful in the treatment or prevention of xenograft rejection comprising combinations of immunosuppressant compounds selected from the group consisting of an IL-2 transcription inhibitor and immunosuppressant compounds that immunosuppress for B-cell-mediated or antibody-mediated rejection of xenografts, and pharmaceutically acceptable diluents or carriers.
2. Pharmaceutical composition comprising combinations of mycophenolic acid (MPA), pharmaceutically acceptable salts and esters of MPA, for example the sodium salt of MPA and the mofetil ester of MPA, rapamycin and derivatives thereof including 40-O-(2-hydroxyethyl)-rapamycin, and IL-2 transcription inhibitors, and pharmaceutically acceptable diluents or carriers.
3. Pharmaceutical composition according to claim 1 or claim 2 comprising mycophenolic acid (MPA) sodium salt and one or more immunosuppressant compounds selected from the group consisting of an IL-2 transcription inhibitor, and rapamycin and derivatives thereof, and pharmaceutically acceptable diluents or carriers.
4. Pharmaceutical composition according to any of the preceding claims comprising MPA sodium salt, cyclosporine and/or 40-O-(2-hydroxyethyl)-rapamycin and pharmaceutically acceptable diluents or carriers.
5. Pharmaceutical composition comprising the combination of an IL-2 transcription inhibitor and an immunosuppressant compound that immunosuppresses for B-cell-mediated or antibody-mediated rejection of xenografts in a weight ratio of about 1:50 to 200:1.
6. Pharmaceutical composition according to any of the preceding claims wherein the weight ratio of MPA sodium salt to cyclosporine is from 1: 0.03 to 1: 0.5.
7. Pharmaceutical composition according to any of the preceding claims wherein the weight ratio of MPA sodium salt to 40-O-(2-hydroxyethyl)-rapamycin is from 1: 0.0005 to 1: 0.015.

8. Use of a pharmaceutical composition as hereinabove described in the manufacture of a medicament for the treatment or prevention of xenograft rejection.
9. A kit of parts comprising a pharmaceutical composition as hereinabove described together with instructions for use in a method as hereinabove described.
10. Pharmaceutical composition and use according to any of the preceding claims wherein the MPA sodium salt is formulated as an enteric-coated solid oral dosage form.

Abstract

A pharmaceutical composition useful in the treatment or prevention of xenograft rejection comprising combinations of immunosuppressant compounds selected from the group consisting of an IL-2 transcription inhibitor and immunosuppressant compounds that immunosuppress for B-cell-mediated or antibody-mediated rejection of xenografts, and pharmaceutically acceptable diluents or carriers.